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**Evaluation of Coronary Artery Disease as a Risk Factor for
Reticular Pseudodrusen.**

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ABSTRACT

Purpose: Reticular pseudodrusen (RPD) is a risk factor for late age-related macular degeneration (AMD). Associations between RPD and coronary artery disease (CAD) have been reported from small case-control studies. This study investigated the association of RPD within a predominantly CAD cohort.

Methods: A subgroup of subjects from a multicenter randomized controlled trial of computed tomography coronary angiography (CTCA) underwent ultra-widefield (UWF) retinal imaging. CAD determined by CTCA was categorized as normal, non-obstructive or obstructive. Specific AMD features in UWF images were graded. Standardized grids were used to record the spatial location of AMD features, including RPD. Multivariate confounder adjusted regression models assessed the association between RPD and CAD.

Results: The 534 participants were aged from 27-75 years (mean 58 ± 9 years; 425 (80%) ≥ 50 years) with a male preponderance (56%). Within the study sample, 178 (33%) had no CAD, 351 (66%) had CAD, 182 (34%) had hypertension and 42 (24%) had neither CAD nor hypertension. RPD was detected in 30 participants (5.6%) and bilaterally in 23. Most participants with bilateral RPD had drusen $>125 \mu\text{m}$ (early AMD). After adjustment for potential confounders (age, sex, drusen $>125 \mu\text{m}$, smoking status), multivariate analysis found no significant association between CAD and RPD (odds ratio [OR] 1.31; 95% Confidence Interval [CI] (0.57-3.01); $p=0.52$). A significant association was identified between RPD and drusen $>125 \mu\text{m}$ (OR 3.18; 95% CI (1.61-6.27); $p=0.001$).

44 **Conclusion:** We found no evidence to support an association between CAD
45 and RPD. RPD was strongly associated with early AMD features, when
46 present.

47 INTRODUCTION

48 Age-related macular degeneration (AMD) is the leading cause of permanent
49 blindness in the developed world with the most sight loss occurring in the late
50 stages, namely geographic atrophy (GA) and choroidal neovascularization (CNV).¹
51 Risk factors for progression from early to late AMD include advancing age,²
52 cardiovascular disease (CVD),³⁻⁵ obesity,⁶ cigarette smoking,⁷ ethnicity,⁸
53 hypertension,³ high cholesterol,⁹ genetic variants such as apolipoprotein E (*ApoE*)
54 gene,¹⁰ age-related maculopathy susceptibility 2 (*ARMS2*) gene,¹¹ complement
55 factor H (*CFH*)¹² and inflammatory markers such as C-reactive protein (*CRP*).¹³
56 Recently, reticular pseudodrusen (RPD) have been shown to be an important
57 independent risk factor for progression to both GA^{14,15} and CNV.^{14,16} In addition,
58 various risk factors have been reported to be associated with RPD including
59 advancing age, female gender, smoking, *ARMS2*, *C3*, *VEGFA* and *CFH* genetic
60 variants.¹⁷⁻¹⁹

61

62 The prevalence of RPD reported in the literature has varied depending on the study
63 design, the extent to which confounding variables are accounted for, and the imaging
64 modality used in its detection. Initial reports of the association came from data
65 collected on AMD cohorts recruited in hospital eye clinics and reported high
66 prevalences ranging from 29 - 52%.^{17, 20-22} Data from population based studies are
67 limited and show large variation, such as 0.4% from the Melbourne Collaborative
68 Cohort study to 4.9% in the Rotterdam study and 13% in the Alienor study.^{18,19,23}
69 Such varying estimates might be attributed to the different imaging and grading
70 protocols used.

71

72 The strong association between RPD and a thin choroid has prompted a spate of
73 small studies that have sought associations between RPD and cardiovascular
74 disease.²⁴⁻²⁸ Cymerman et al reported in a small prospective cohort of patients with
75 no known retinal disease recruited from a cardiovascular clinic; 23 participants with
76 coronary artery disease (CAD) had a higher frequency of RPD compared to 15 who
77 did not have CAD.²⁴ A literature review by Rastogi and Smith²⁵ on the association
78 between AMD, RPD with CVD highlighted studies reporting an association between
79 RPD and hypertension and angina.²⁶⁻²⁹ Smith and colleagues hypothesized that the
80 increased mortality from systemic-vascular disease that affects males more severely
81 compared to females, may account for the higher proportion of women with RPD that
82 has been observed in various population-based studies.²⁹ Notably this review
83 highlighted the potential importance of large prospective cohort studies sampling
84 participants >45 years with and without CAD to identify RPD development and
85 potential associations.²⁵

86

87 A sub-study of the SCOT-HEART (SH) trial that incorporated ultrawide field (UWF)
88 retinal imaging offered a unique opportunity to explore the relationship between CAD
89 and RPD. The use of widefield technology to evaluate the retinal fundus offered an
90 additional advantage as RPD is commonly located in the retinal arcades and beyond
91 ²⁶ and to date there is only one study that has estimated RPD prevalence that has
92 included central and peripheral retinal locations.³⁰ However the sensitivity of UWF to
93 detect RPD has not been established. We therefore first validated the methodology
94 using images from a population based epidemiological study (the Northern Ireland
95 Cohort of Longitudinal Ageing [NICOLA]) which captured both UWF, CFP, OCT,

96 infra-red and autofluorescence (AF) images of the retina and subsequently used the
97 SH trial sub-study UWF images to explore the relationship between RPD and CAD.

98

99 **MATERIALS AND METHODS**

100 **Validation of detection of RPD by UWF imaging**

101 Nine hundred consecutive participants were selected from the NICOLA Study. CFP
102 was performed on the Canon CX-1 Digital Fundus Camera (Canon U.S.A., Inc.,
103 Melville, NY, U.S.A.). Stereoscopic pairs centered on the optic disc and macula were
104 captured. CFP images were viewed and graded using the Oculab program (Digital
105 Healthcare Oculab, V3.7.98.0, Emis Health, Leeds, UK). UWF retinal imaging was
106 performed on the Optos Tx200 Scanning Laser Ophthalmoscope (Optos PLC,
107 Dunfermline, UK) using both color and AF acquisition modes. Images were viewed
108 and graded using the Optos V² Vantage Pro software (version 2.9.4.2). OCT images
109 were captured using the Heidelberg Spectralis SD-OCT/SLO (Heidelberg
110 Engineering, Heidelberg, Germany). Images were reviewed using the Heidelberg
111 eye explorer, HEYEX software version 1.9.10.0. Multimodal grading was undertaken
112 with display of the multicolor enface retinal image (includes infrared reflectance,
113 green reflectance and blue reflectance) centered on the fovea. The grading
114 distinguished the reticulated pattern visible on the en face images which were
115 classified as RPD from subretinal drusenoid deposits (SDD) which are the OCT
116 correlate seen on the high resolution OCT B scans. This distinction was made as
117 mild and subtle features of SDD can be present before RPD are seen on the en face
118 imaging modalities.

119 UWF images were graded for the presence or absence of RPD by a trained single
120 grader who was not involved in any other grading procedures with quality assurance

and review by a retina specialist (UC). Multimodal (CFP, MultiColor, AF and OCT images) grading was undertaken by trained graders in the network of UK Reading Center's (NetwORC UK) for the presence or absence of RPD. Detection of RPD on any modality was taken as evidence of presence of this feature. Sensitivity and specificity of the UWF imaging in detecting RPD compared to the RPD detected from the NICOLA cohort's *en face* images was computed.

The SCOT-HEART (SH) Study and Sample

The SH trial (ClinicalTrials.gov, number NCT01149590) was a multicenter randomized controlled trial undertaken in Scotland (2010-2014) on 4,146 participants, aged 18-75 years, drawn from 12 cardiology clinics across Scotland.³¹ The main aim of the study was to determine the role of multidetector computed tomography in the diagnosis and management of patients attending rapid access chest pain clinics. Participants were randomly assigned to either standard care (control intervention) or standard care and the computed tomography coronary angiography (CTCA) and calcium scores (intervention). CAD was categorized in the SH study as: (i) obstructive CAD, atherosclerotic plaque encompassing a luminal cross-sectional area of $\geq 70\%$ in at least one major epicardial vessel; (ii) non-obstructive CAD, either atherosclerotic plaque encompassing a luminal cross-sectional area of $< 70\%$ but $> 10\%$ in at least one major epicardial vessel, or a calcium score > 400 AU (Agatston units) or > 90 th percentile for age and sex; or (iii) minimal or no CAD. Non-obstructive disease was further sub-divided into mild (10-50% luminal cross-sectional area) or moderate (50-70% luminal cross-sectional area) stenosis. At two sites (Edinburgh and Dundee), consecutive patients were

approached to undergo UWF imaging immediately before or after undergoing CTCA. We assessed 534 participants from a sub-study of SH who had UWF imaging captured using two Optos P200C Scanning Laser Ophthalmoscopes (Optos PLC, Dunfermline, UK) in addition to the normal study procedures at two sites (the Clinical Research Imaging Center in Edinburgh and the Clinical Research Center Dundee).³²

Image Grading in SH

Specific features of AMD in UWF images were graded for AMD characteristics (increased pigment, decreased pigment, drusen, maximum drusen size, reticular pseudodrusen, GA and CNV) and other peripheral abnormalities using the 'Study-specific Grading Procedures for OPERA Study,' guidelines (November 2013).³³ The Optos software utilised a modified Studies of Ocular Complications of AIDS (SOCA) optos peripheral retina AMD study (OPERA) grid (Figure 1) which was divided into three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed on the SOCA grid to estimate the ungradable areas (Figure 2). In accordance with the OPERA guidelines, at least 50% of the subfield should be visible to grade; if < 50% of the subfield was visible, it was graded as "Cannot Grade." If AMD characteristics and other pathologies were present in a Cannot Grade subfield, and if the grader was $\geq 90\%$ certain the lesion was present, then grading was ascribed. Drusen presence was graded as follows: absent; questionable; 1-5 drusen; 6-20 drusen; >20 drusen or cannot grade. The maximum drusen size was graded as follows: < 125 μm ; $\geq 125\mu\text{m}$, < 250 μm distinct; $\geq 125\mu\text{m}$, < 250 μm indistinct; $\geq 250\mu\text{m}$ distinct; $\geq 250\mu\text{m}$ indistinct or cannot grade. RPD was graded as follows: absent; questionable; < 25% of subfield; 25-49% of

subfield; 50-74% of subfield; $\geq 75\%$ of subfield or cannot grade. RPD were defined as yellow interlacing networks ranging from 125 μm to 250 μm in width or lesions that occurred in regular well-defined domains (Figure 3). Images in which RPD were questionable were arbitrated by a retinal specialist (UC).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 20 (Portsmouth, UK). Intraobserver agreement was calculated after 1 in 20 of the images were randomly regraded for RPD and drusen using kappa (k) statistics, which express the extent of agreement beyond chance. The interpretation of the k statistic was as follows: 0, no agreement; 0 to 0.2, slight agreement; 0.21 to 0.40, fair agreement; 0.41 to 0.60, moderate agreement; 0.61 to 0.8, substantial agreement; and >0.81 , almost perfect agreement.³⁴

Univariate analysis (Chi-squared test or Fisher's exact test for categorical variables and independent t-test for continuous variables) was used to examine differences in the demographic characteristics of participants according to presence or absence of RPD. General estimating equations (GEE) which enabled data from both eyes to be included were used to examine the association between RPD and CAD while accounting for other factors identified as significant from the univariate analysis.

RESULTS

Validation study

UWF imaging detected 8 participants with reticular drusen (2 unilateral and 6 bilateral; 100% sensitivity).. Multimodal imaging (color, multicolor, infra-red and autofluorescence) detected reticular drusen in 7 of those which were seen on *en face* images The specificity of the UWF imaging was 99.9%. In one case, the UWF imaging detected RPD beyond the field of view captured by the combination of retinal imaging (Figure 4). The positive predictive value (PPV) was calculated at 87.5% and the negative predictive value (NPV) was 100%.

Participant Characteristics in SH study

Table 1 summarizes SH study participant characteristics. In total 534 individuals had UWF retinal images captured. Two participants [4 eyes] proved difficult to scan and images were not obtained. This left 532 pairs of eyes for grading. The mean age was 58 years (range=27-75, SD 9.5) with 425 (80%) aged over 50 years. There were 299 males (56%). 178 (33%) had no CAD, 351 (66%) had CAD present, whilst 182 (34%) had hypertension and 42 (24%) had no CAD or hypertension.

Intragrader agreement in SH study

The intragrader agreement illustrated in Table 2 gives the kappa range for the AMD features, the presence of RPD ranged from: 0.62-0.76, drusen: 0.58-0.64, maximum drusen size: 0.55-0.62, increased pigment: 0.54-0.61, decreased pigment: 0.55-0.62, GA: 0.62-0.76, neovascular AMD: 0.57-0.66 and peripheral abnormality: 0.55-0.59 within zones 1-3. For the lesions which were absent in the cohort the discordance in the grading originated from a change of grade of feature absent to ungradeable between the two gradings.

218

219 **Prevalence of RPD and AMD features in the SH study**

220 RPD was present in one or both eyes of 30 participants (5.6%) and bilateral in 23
221 participants (4.3%). Drusen $>125\mu\text{m}$ were present in 201 participants (38%).
222 Participants with RPD ranged in age from 33-75 years (mean 59) and there were
223 equal numbers of males and females. The other AMD features graded as present in
224 the participants were as follows: 352 (66%) had hyperpigmentation, 55 (10%) had
225 hypopigmentation, 2 (0.4%) had unilateral GA, none of the participant was classified
226 as having neovascular AMD and 183 (34%) showed other non-AMD peripheral
227 abnormalities.

228

229 **Association of CAD with RPD**

230 CAD was present in 20 participants and absent in 10 participants with RPD,
231 however, no statistically significant association between RPD and CAD was found on
232 either the unadjusted or adjusted generalized estimating equations (GEE) model
233 ($p>0.05$, Table 3). With respect to associations between RPD and other early AMD
234 features a strong association was noted with drusen $>125\mu\text{m}$ in the fully adjusted
235 model. Eighteen participants had both RPD and drusen $>125\mu\text{m}$, while 11
236 participants had RPD alone without evidence of soft drusen.

237

238 **DISCUSSION**

239 This is the first study to report the prevalence of RPD from a cohort drawn from a
240 cardiovascular clinical setting which had also captured UWF retinal images thus
241 allowing an examination of potential associations. Contrary to previous reports, we
242 failed to find a significant association between RPD and the presence of

anatomically defined CAD.^{24-27,29} Our findings are in accordance with population based studies and some of the clinical cohorts that did not report significant associations between RPD and CAD or hypertension.^{17-19,21-23} In fact, the prevalence of RPD observed in the current study (30 out of 534 participants - 5.6%) is similar to that reported by the population based Rotterdam study (4.9%),¹⁸ providing additional support for the view that CAD is not associated with an increased prevalence of RPD.

While 80% of participants were aged over 50, a common age restriction for many AMD studies, interestingly 8 participants with RPD were aged under 50, the youngest aged 33. Of these 4 (50%) also had evidence of drusen >125µm whereas the rest had no other features of AMD present. In the overall sample, 7 participants had RPD without any other AMD features similar to previous observations,¹⁸ which may reflect a different phenotype given that RPD have been reported in other retinal diseases such as Sorsby fundus dystrophy, pseudoxanthoma elasticum and acquired vitelliform lesions.³⁵⁻³⁷ Given the rarity of these participants, it is likely that studies of large sample size or pooled analyses across studies will be required to improve our understanding of the relevance of these isolated RPD.

This is also the second study, to our knowledge, that used UWF imaging for the evaluation of RPD.³⁰ The validation protocols implemented using NICOLA image data confirmed the reliability of this approach to detect the reticular pattern that has been observed when using other *en face* modalities such as IR or AF imaging. Nonetheless we are of the view that as with other *en face* modalities color UWF also underestimates the prevalence because the earliest stages of this phenotype of SDD

is best appreciated on high resolution SD OCT.³⁸ Stage one SDD is defined by the dispersed nature of the deposits of granular hyperreflective material that is present in the outer retina in the region of the photoreceptors' inner and outer segments (the IS/OS boundary) and the retinal pigment epithelium, prior to the characteristic reticulated pattern that accompanies stages 2 and 3, which have been attributed to focal deposits that cause marked alterations to the IS/OS boundary and thus become detectable by en face imaging.³⁸ Currently it is accepted that detection of RPD is best when a multimodal approach, combining infra-red reflectance, AF and SD-OCT are used.^{23,39} We were however reassured by the validation study which demonstrated the benefit of the increased field of view provided by UWF imaging and that RPD was evident in at least one participant in the retinal fundus in an area that is typically not evaluated in AMD studies using CFP (35° or 45°), raising the possibility of under ascertainment when the evaluated images are restricted to the central fundus.

A potential limitation of this study is the choice of controls and the few RPD cases, as all recruits were attending the cardiology clinic for suspected angina. However the trial participants were recruited from a Chest pain clinic, and they were subsequently classified as having no CAD on the basis of clinical examination, computed tomography coronary angiography and calcium scores. Whether this cohort is representative of what may be observed in a random population based sample is unclear. Even though we adjusted for age, sex and the presence of smoking, given the focus of the SH trial, some of the traditional AMD risk factors, such as diet and known genetic risk variants, were not available and therefore residual confounding may be present.

293

294 In conclusion, our study does not support previously reported associations with CAD,
295 yet the strong association observed with other AMD features in this non-AMD cohort
296 highlights the necessity for improved understanding of the mechanisms and
297 ethiology of this intriguing phenotype. To do so, more data from large and well
298 characterized longitudinal population based studies with multimodal imaging will be
299 required. addition, pooled analyses of multiple studies to improve statistical power
300 may help untangle the complexity of the risk factors and sub-phenotypes involved.

301

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316

317

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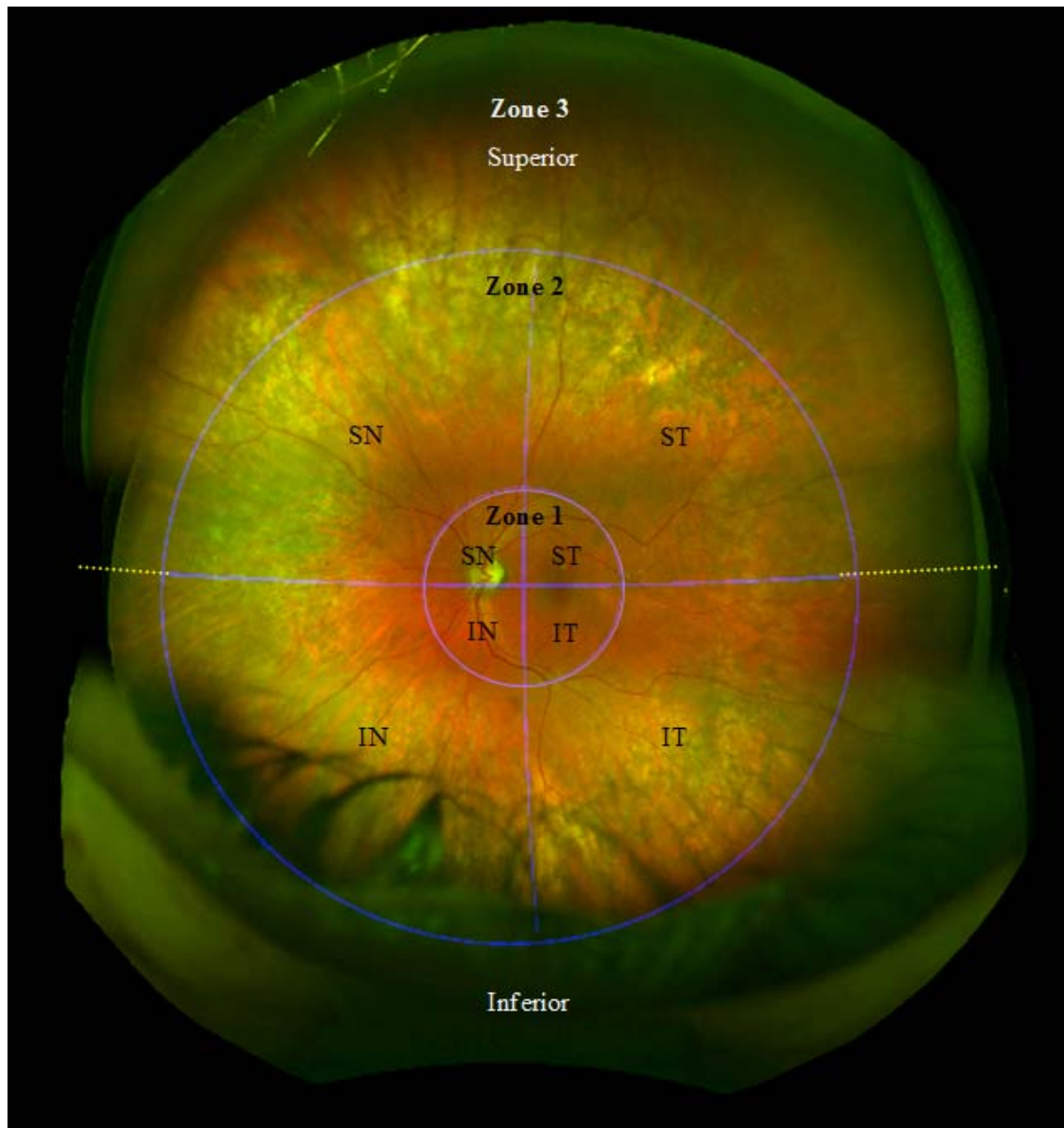
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430

431 **Figure 1: The Modified SOCA Grid utilized on the Optos Software.**

432 Z1 and Z2 are each divided into four quadrants: superonasal (SN), superotemporal
 433 (ST), inferotemporal (IT), and inferonasal (IN). Z3 is divided into two hemispheres
 434 (superior, inferior) using a visual extension of the horizontal cross line (yellow
 435 dashed lines). Taken from the Study-Specific Grading Procedures for OPERA,
 436 University of Wisconsin (2013).³³

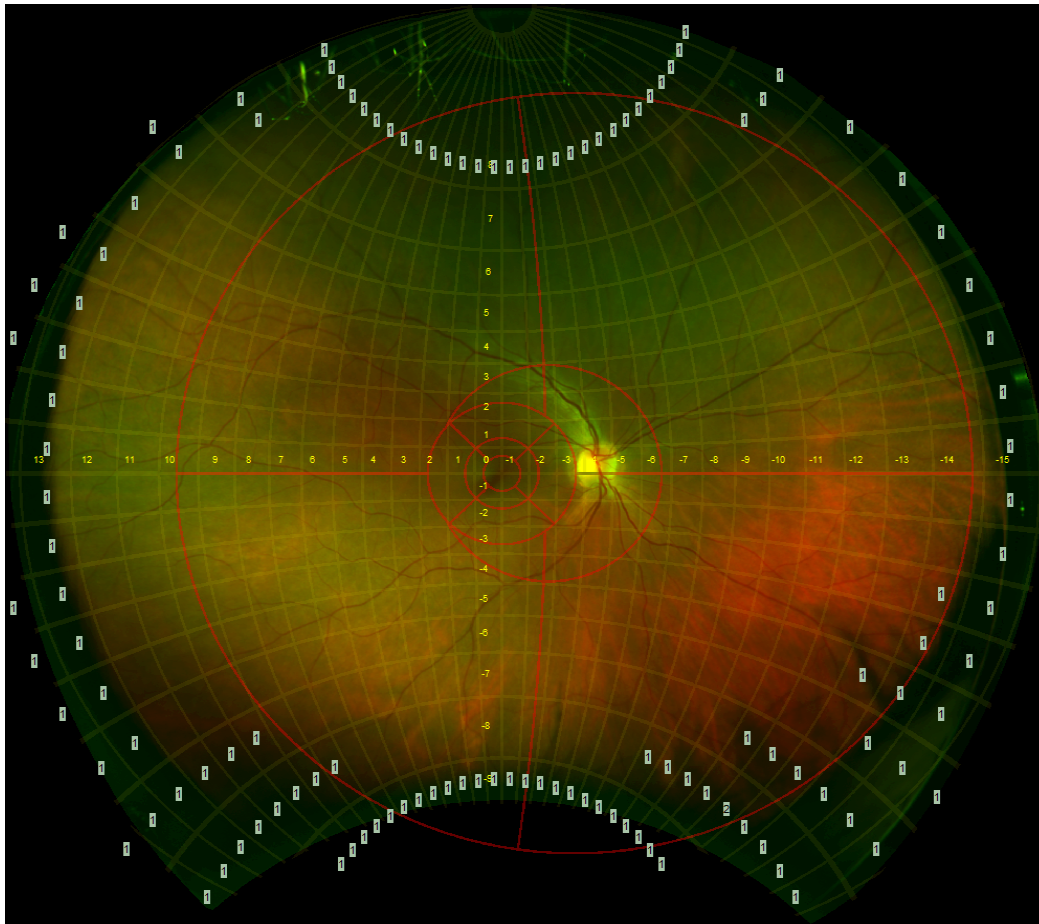
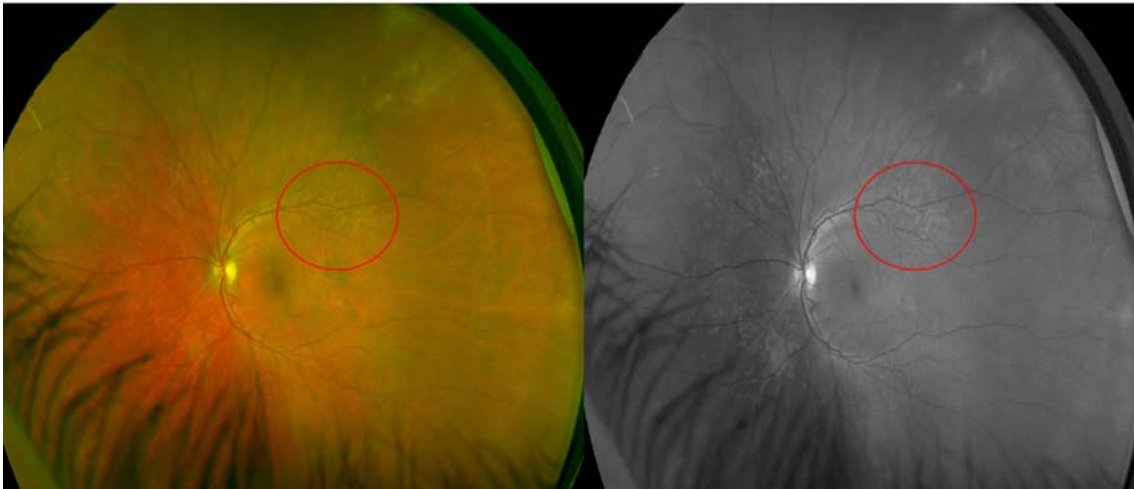


Figure 2: Optos ultra-widefield retinal image grading grids for specific AMD characteristics.

The SOCA grid is divided into three zones: Zone 1 (posterior pole), Zone 2 (extends from Z1 to a circle through the ampullae of the vortex veins) and Zone 3 (extends from Z2 to the outer periphery). The Manchester grid was superimposed onto the SOCA grid to assess the ungradable areas.

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446

447 **Figure 3: Optos ultra-widefield retinal image illustrating RPD.**

448 RPD is a subtype of AMD associated with subretinal drusenoid deposits located
449 between the retinal pigment epithelium and the inner ellipsoid zone.

450

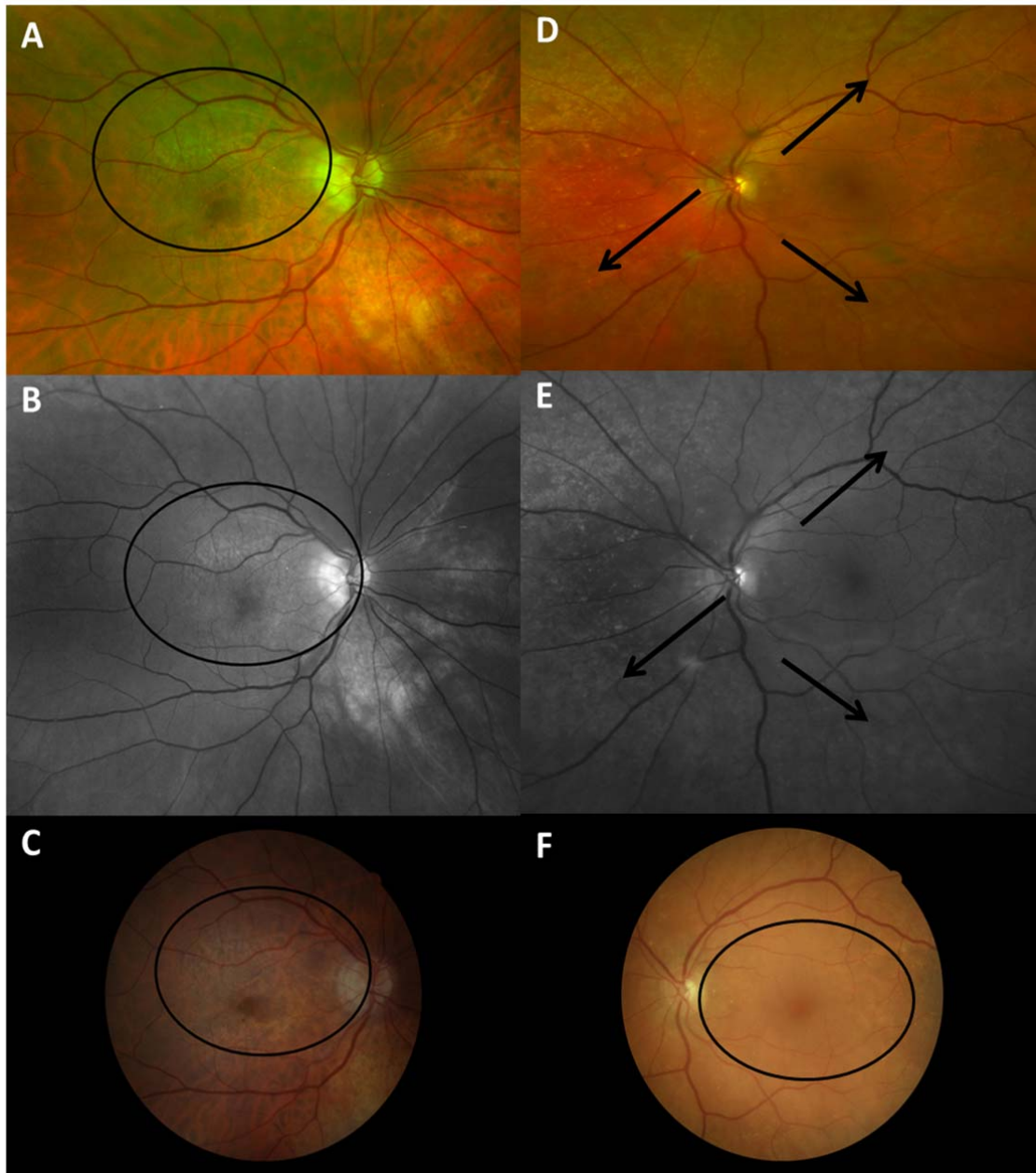


Figure 4 shows the RPD interlacing pattern on both the UWF and fundus camera image. **A.** UWF pseudo color image showing RPD (black circle). **B.** UWF green laser imaging with RPD visible within the black circle. **C.** Fundus camera image with RPD within the black circle. **D.** UWF pseudo color image with arrows pointing to areas of RPD. **E.** UWF green laser imaging with arrows annotating areas of RPD. In this case RPD was detected beyond the field of view of color fundus photography. **F.**

458 Corresponding fundus camera image with no readily visible RPD within the black
459 circle.

Table 1. Summary statistics for study participants.

	All participants N=534	Reticular Pseudodrusen (1 or both eyes)		
		Absent N=504	Present N=30)	P
Age Mean (SD)	58 (10)	58 (9)	59 (12)	0.76
Sex (%) Male Female	299 (56) 235 (44)	284 (56) 220 (44)	15 (50) 15 (50)	0.57
BMI Mean (SD)	30 (7)	30 (7)	28 (6)	0.19
CAD diagnosis (%) None Non-Obstructive-Mild Non-Obstructive-Moderate Obstructive CAD Missing	178 (33) 114 (21) 87 (16) 150 (28) 5 (1)	168 (33) 105 (21) 84 (17) 142 (28) 5(1)	10 (33) 9 (30) 3 (10) 8 (27) 0 (0)	0.71
CAD (%) Absent Present Missing	178 (33) 351 (66) 5 (1)	168 (33) 331 (66) 5 (1)	10 (33) 20 (67) 0 (0)	0.99
Assign Score Mean (SD)	18 (12)	18 (12)	17 (11)	0.56
Coronary Artery Calcium Score Mean (SD)	314 (805)	310 (814)	376 (634)	0.67
Hypertension (%) No Yes Missing	346 (65) 182 (34) 6 (1)	327 (65) 171 (34) 6 (1)	19 (63) 11 (37) 0 (0)	0.84
Diabetes (Type1 or 2) (%) No Yes	483 (90) 51 (10)	455 (90) 49 (10)	28 (93) 2 (7)	0.76
Drusen >125µm (%) Absent Present Missing	330 (62) 201 (38) 3 (1)	319 (63) 183 (36) 2 (1)	11 (37) 18 (60) 1 (3)	0.01
Smoking History (%) Never Ex-smoker Current Smoker	256 (48) 193 (36) 85 (16)	244 (48) 183 (36) 77 (15)	12 (40) 10 (33) 8 (27)	0.25

464 **Table 2.** Intragrader agreement for the individual age-related macular
 465 degeneration phenotypes.

AMD Characteristic	Kappa Range		
	Zone 1	Zone 2	Zone 3
Neovascular AMD	0.66	0.57	0.61
Increased Pigment	0.59	0.54	0.61
Decreased Pigment	0.66	0.55	0.62
Geographic Atrophy	0.66	0.76	0.62
Drusen	0.59	0.64	0.58
Maximum Drusen Size	0.60	0.62	0.55
Reticular Pseudodrusen	0.67	0.76	0.62
Peripheral Abnormality	N/A	0.59	0.55
Presence of other Pathology (All zones)	0.62		

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467

Table 3 – Investigation of coronary artery disease as a risk factor for reticular pseudodrusen using generalized estimating equations.

	Unadjusted model			Age and Sex adjusted			Multivariate adjusted*		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
CAD	1.30	0.58-2.92	0.52	1.33	0.57-3.11	0.52	1.31	0.57-3.01	0.52
Age				1.01	0.95-1.07	0.78	1.00	0.95-1.06	0.92
Sex				1.51	0.67-3.40	0.32	1.40	0.62-3.14	0.42
Drusen >125 μm							3.18	1.61-6.27	0.001

*Multivariate model was adjusted for age, sex and smoking status.